Targeted Research Area: Childhood Cancers

General Information on Childhood Cancers

- **Prevalence and incidence of childhood cancers:**
  - Approximately 8,600 U.S. children between the ages 0 and 14 will be diagnosed with cancer in 2002, according the American Cancer Society and SEER Cancer Statistics Review. Overall, childhood cancer rates have increased nearly 21% from 1975 to 1998 and appear to be increasing at approximately 1% every year. [25]
  - About one third of childhood cancers are leukemias; approximately 2,700 children (<age 15) were diagnosed with leukemia in 2001. [26]Acute lymphocytic leukemia (ALL) and brain tumors have increased particularly in children 0 to 5 years old.[27]
  - Childhood cancer rates have increased nearly 21% from 1975 to 1998 and are increasing at a steady rate of approximately 1% per year.[28]
  - Nearly 12,000 children under the age of 19 are diagnosed with cancer each year in the U.S. The most frequently diagnosed childhood cancers include leukemias, CNS tumors, neuroblastoma, Hodgkin's disease, non-Hodgkin's lymphoma, Wilms' tumor, retinoblastoma, soft tissue sarcomas, and germ cell tumors. The incidence of ALL has been increasing at about 1% per year; incidence of CNS tumors has increased at about 1.5% per year.[29]

- **Mortality from childhood cancers:**
  - Cancer is the leading cause of death from disease in children under 15 and the second leading cause of death in most age groups.[30]
  - The most common tumors in infancy and childhood are neuroblastoma, leukemia, and renal tumors, resulting in about 10,000 cancer deaths per year in the U.S.

- **Disease severity/disease burden:** This information was not readily available to The Lewin Group.

- **Cost to individual/family/society/healthcare system:** This information was not readily available to The Lewin Group.

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[25] Massey-Stokes M, Lanning B. Childhood cancer and environmental toxins: The debate continues. Family & Community Health 2002;24(4):27-38.

[26] National Cancer Institute, National Institutes of Health. Cancer Facts: National Cancer Institute Research on Childhood Cancers. Available at: http://cis.nci.nih.gov/fact/6_40.htm

[27] Massey-Stokes M, Lanning B. Childhood cancer and environmental toxins: The debate continues. Family & Community Health 2002;24(4):27-38.

[28] Bowman P, Oblender M, Oeffinger KC, Ward J. Childhood cancer and environmental toxins: the debate continues. Family & Community Health 2002;24(4):27-38.

[29] Ross JA, Swensen AR. Prenatal epidemiology of pediatric tumors. Current Oncology Reports 2000;2(3):234-41.

[30] Bowman P, Oblender M, Oeffinger KC, Ward J. Childhood cancer and environmental toxins: the debate continues. Family & Community Health 2002;24(4):27-38.

- **Frequency/load of exposure:** The frequency / load of exposure varies depending on the type of exposure and associated disease outcome.

- **Special populations:** Special populations in which either the exposure or disease outcome or both are more prevalent vary.

Hypotheses 6 – 10, described on the following pages, are associated with the Childhood Cancers targeted research area.

Hypothesis #6: Exposure to electromagnetic fields (EMFs) may increase the risk of childhood cancers such as leukemia (acute lymphocytic and T-cell) and brain tumors.

General Information Related to Hypothesis #6

- **Frequency/load of exposure to EMFs**: Residential and industrial use of electricity for power, heating, and lighting has increased exposure to EMF in the past few decades.
- **Special populations:** Jobs that place workers near high-voltage substations and electricity should receive attention regarding occupational exposure related diseases.
- **Findings from recent research (targeted search):** Information reported in the following five studies study contributed to the above-mentioned hypothesis.

Study #1: Ahlbom IC, Cardis E, Green A, Linet M, Savitz D, Swerdlow A. Review of the epidemiologic literature on EMF and Health. Environmental Health Perspectives 2001;109(Suppl 6):911-33.

Study #1 hypothesis being tested: EMF exposure is a possible risk factor for chronic diseases, including childhood cancer such as leukemia, and may also affect other endpoints including pregnancy outcomes.

Study #1 findings: Some studies have indicated an association between postnatal exposures above 0.4 µT and childhood leukemia. The mechanism by which exposure could lead to cancer, however, is unknown. Current evidence does not support hypothesis that maternal exposure to residential or occupational EMF is associated with adverse pregnancy outcomes. There is no chronic disease outcome for which an etiological relation to EMF exposure can be regarded as established. Childhood leukemia in relation to postnatal exposure has been most evident of an association.

Study #2: Schuz J, Grigat JP, Brinkmann K, Michaelis J. Residential magnetic fields as a risk factor for childhood acute leukemia: results from a German population-based case-control study. International Journal of Cancer 2001;91(5):728-35.

Study #2 hypothesis being tested: Exposure to residential power-frequency (50 Hz) magnetic fields above 0.2 µT increases risk of childhood leukemia. Risk is increased with exposure to stronger magnetic fields during the night.

Study #2 findings: The study found evidence of a weak association between exposure to residential magnetic fields, in general, and leukemia. There was, however, a significant association between childhood leukemia and magnetic field exposure at night. The authors suggest that although there is evidence of an association between leukemia and exposure to magnetic fields, this association neither proof nor a breakthrough. Evidence of an association with magnetic field exposure at night may warrant further study. Increased leukemia risk from night exposure to magnetic fields may be due to suppression of nocturnal production and release of melatonin which is assumed to have

oncostatic capabilities. Another hypothesis that might account for any association is that children with prenatal genetic abnormalities require a postnatal event such as exposure to magnetic fields for full development of leukemia.

Study #3: Bowman P, Oblender M, Oeffinger KC, Ward J. Childhood cancer and environmental toxins: the debate continues. Family & Community Health 2002;24(4):27-38.

Study #3 hypothesis being tested: Exposure to environmental toxins and other risk factors (e.g., EMFs, radon, pesticides, solvents, parental occupational exposure, diet, ETS, alcohol, and infection during preconception, in utero, and postnatal periods) can lead to an increased risk of childhood cancers, particularly acute lymphocytic leukemia (ALL) and brain tumors.

Study #3 findings: The links between many environmental agents, including EMFs, radon, pesticides, solvents, parental occupational exposure, diet, ETS, alcohol, and infection, and cancers such as leukemia remain speculative. The authors suggest that childhood cancers are most likely a result of an interaction between genetic predisposition, environmental factors, and susceptibility. The authors call for further studies focused on genetic predisposition.

Study #4: Bolande RP. Prenatal exposures and childhood cancer. Pediatric and Developmental Pathology 1999;2(3):208-14.

Study #4 hypothesis being tested: Some childhood cancers are initiated in the embryo, fetus, or parental germ cells as a result of prenatal or preconceptional exposures to electromagnetic fields, paint, hydrocarbon, cigarette smoke, etc.

Study #4 findings: The study discusses findings from research on environmental toxicants as causal factors for childhood cancers. DES, for example has been identified as a transplacental carcinogen. HTLV, an oncogenic retrovirus, has been shown to be transmittable from mother to child through breast milk and can lead to T-cell leukemia. The authors found that no specific parental occupation or exposure or etiologic agent has been firmly established that could preconceptionally initiate or cause a childhood cancer. Prenatal carcinogenicity of irradiation remains unclear and controversial; studies have varied in success in showing an association of childhood tumors and prenatal exposure to ionizing irradiation. Heritable factors are important in less than 10% of childhood tumors. Most are the result of environmental carcinogenic agents which have yet to be identified. The authors suggest that genetic susceptibility, host resistance, and the embryonic environment may also play a role in childhood cancers.

Study #5: Ross JA, Swensen AR. Prenatal epidemiology of pediatric tumors. Current Oncology Reports 2000 May;2(3):234-41.
(Note: This study is cited under childhood cancers and other exposures – infectious agents and paternal/maternal smoking.)

Study #5 hypothesis being tested: Infectious agents such as mycoplasma pneumonia and hepatitis A may lead to leukemia. There may be a dose-response relationship in the

association between in utero exposure to radiation and childhood leukemia. Paternal smoking has a more powerful effect on childhood cancer than maternal smoking. EMF exposure may be associated with leukemia.

Study #5 findings: One study in Greece indicated that infants exposed in utero to radiation had a higher incidence of leukemia and that there was a positive dose-response relationship between incidence and radioactivity in the region. Most epidemiological studies of parental smoking have indicated positive associations between paternal, rather than maternal, smoking and childhood cancer. This may be due to germ cell mutations in the father that develop before conception. Studies have not been able to show a significant association between EMF exposure and childhood cancer. It is probable that prenatal and postnatal exposure to low frequency EMFs through power lines or small appliances is not strongly associated with an increased risk of leukemia. No individual data has yet been collected to support or refute hypotheses involving the association between infectious agents and childhood cancer. The etiology of most cancers is unknown. The prenatal period is emerging as the etiologically relevant window for many childhood, particularly infant cancers. The association between maternal exposure to farm animals and development of brain tumors in children needs further research. Medical exposure to medications such as metronizadole in utero may be linked to childhood cancer. One study found an increased risk of neuroblastomas in children exposed to this drug in utero. Further studies may be needed given some outcomes may not appear until later in childhood or adolescence.

Hypothesis #7: Exposure to solvents and paints may increase the risk of childhood cancers, including leukemia and brain tumors.

General Information Related to Hypothesis #7

- **Findings from recent research (targeted search):** Information reported in the following two studies contributed to the above-mentioned hypothesis.

Study #1: Colt JS, Aaron B. Parental occupational exposures and risk of childhood cancer. Environmental Health Perspectives 1998;106:909-925.

Study #1 hypothesis being tested: Paternal occupational exposure to solvents, paints, and motor vehicles may cause cancer in offspring.

Study #1 findings: The study found that evidence for an association between childhood leukemia and paternal exposure to solvents is strong; elevated risk was found between diverse occupations related to motor vehicles or involving exposure to exhaust gases and childhood leukemia; and results on the relationship between paternal exposure to ionizing radiation and childhood leukemia/lymphoma have varied. The authors state that assessing exposures to specific workplace agents is problematic when the only available information is a job or industry title, as is the case with most studies conducted to date. Workers with identical job titles can have different exposures depending on specific activity or task. Also, the timeframe of exposure is difficult to assess, i.e., whether exposure is prior to conception, during pregnancy, from exposure experienced at the workplace or from transfer of substances to the home, or after birth. Small numbers of exposed cases in studies of occupation and child cancer make it difficult to achieve stable results. Aggregating different jobs may increase numbers but also increase misclassification of exposures. Evidence from experimental investigations and epidemiologic studies of adult cancer and occupational exposure suggests that an association between fathers' occupations and the risk of childhood cancer is plausible. Furthermore, more research is needed on the association of childhood cancer and maternal occupations in textiles that use dyes, organic dusts and fibers, and EMF.

Study #2: Bowman P, Oblender M, Oeffinger KC, Ward J. Childhood cancer and environmental toxins: the debate continues. Family & Community Health 2002;24(4):27-38.*

Study #2 hypothesis being tested: Exposure to environmental toxins and other risk factors (e.g., EMFs, radon, pesticides, solvents, parental occupational exposure, diet, ETS, alcohol, and infection during preconception, in utero, and postnatal periods) can lead to an increased risk of childhood cancers, particularly acute lymphocytic leukemia (ALL) and brain tumors.

Study #2 findings: Many environmental agents, including EMFs, radon, pesticides, solvents, parental occupational exposure, diet, ETS, alcohol, and infection, that are cited as causes of cancers such as leukemia, remain speculative. The authors suggest that childhood cancers are most likely a result of an interaction between genetic predisposition, environmental factors, and susceptibility. The authors call for further studies focused on genetic predisposition.

Hypothesis #8: Exposure to insecticides/pesticides may increase the risk of childhood cancers, including leukemia and lymphomas.

General Information Related to Hypothesis #8

- **Findings from recent research (targeted search):** Information reported in the following two studies contributed to the above-mentioned hypothesis.

Study #1: Meinert R, Schüz J, Kaletsch U, Kaatsch P, Michaelis J. Leukemia and non-Hodgkin's lymphoma in childhood and exposure to pesticides: results of a register-based case-control study in Germany. American Journal of Epidemiology 2000;151:639-646.

Study #1 hypothesis being tested: Exposure to insecticides used residentially, pesticides used on farms and gardens, and parental occupational pesticide exposure may be related to childhood cancer.

Study #1 findings: The study found an association between use of household insecticides and extermination of insects by professional pest controllers and lymphomas. Evidence of a link between pesticides and leukemia and lymphoma was weaker; the use of pesticides in gardens was not related to childhood leukemia and lymphoma, but use of pesticides on farms was weakly associated with childhood leukemia.

Study #2: Massey-Stokes M, Lanning B. Childhood cancer and environmental toxins: The debate continues. Family & Community Health 2002;24(4):27-38.+

Study #2 hypothesis being tested: Childhood cancers are linked to exposure to environmental toxins such as insecticides and pesticides.

Study #2 findings: The authors note that whether increases observed are truly due to cancer linked to environmental toxicant exposure or better diagnosis or more thorough reporting is unclear. Due to linkages between pesticides, diet, and insecticides, causes of childhood cancer are difficult to identify. Proving the causative nature of environmental toxins is difficult due to exposure estimation from personal memory recall or interview responses. Genetic susceptibility to some cancers has increased interest in biomarker research. However, except for families with a strong history of cancer, the strength of predictability with genetic biomarkers has been inconclusive.

Hypothesis #9: Exposure to paternal/maternal smoking may increase the risk of childhood cancers, including brain tumors, and may increase the risk of lung cancer in adulthood.

General Information Related to Hypothesis #9

- Primary central nervous system tumors are the leading cause of cancer related death among children less than 15 years of age. Such tumors account for approximately 20% of malignancies in this age group.[31]
- Cigarette smoking has been identified as a major source of preventable morbidity and premature mortality. Animal studies suggest that some effects of exposure in early life may not be apparent until adult life.[32]
- **Findings from recent research (targeted search):** Information reported in the following three studies contributed to the above-mentioned hypothesis.

Study #1: Huncharek M, Kupelnick B, Klassen H. Paternal smoking during pregnancy and the risk of childhood brain tumors: Results of a meta-analysis. 2001;15:535-542.

Study #1 hypothesis being tested: Paternal smoking during pregnancy may be associated with increased risk of brain tumor development in the offspring.

Study #1 findings: A meta-analysis of numerous studies published in the literature - enrolling a total of 3,600 patients - demonstrated a statistically significant result suggesting an approximately 29% increased risk of brain tumor development associated with paternal smoking during pregnancy versus children of non-smoking fathers. Epidemiological data suggest that an association between paternal smoking during pregnancy and brain tumor development is biologically plausible. Transplacental migration of tobacco specific carcinogens to the fetus from ETS from the father's smoking during pregnancy poses a risk to the unborn child. However, the etiology of central nervous system tumors is yet unknown.

Study #2: Boffetta P, Tredaniel J, Greco A. Risk of childhood cancer and adult lung cancer after childhood exposure to passive smoke: a meta-analysis. Environmental Health Perspectives 2000;108(1):73-82.

Study #2 hypothesis being tested: Childhood exposure to maternal smoking increases risks for childhood cancer and adult lung cancer.

Study #2 findings: Childhood exposure to maternal smoking increases risks for childhood cancer and adult lung cancer. Meta-analysis showed a 10% increased risk of childhood cancer as a result of exposure to maternal smoke. However, the increase in

[31] Huncharek M, Kupelnick B, Klassen H. Paternal smoking during pregnancy and the risk of childhood brain tumors: Results of a meta-analysis. 2001;15:535-542.

[32] Boffetta P, Tredaniel J, Greco A. Risk of childhood cancer and adult lung cancer after childhood exposure to passive smoke: a meta-analysis. Environmental Health Perspectives 2000;108(1):73-82.

risk is small and may be explained by bias and confounding. In addition, studies have not shown a significant increased risk of adult lung cancer from exposure to passive smoking in childhood.

Study #3: Ross JA, Swensen AR. Prenatal epidemiology of pediatric tumors. Current Oncology Reports 2000 May;2(3):234-41.
(Note: This study is cited under childhood cancers and other exposures – EMFs and infectious agents.)

Study #3 hypothesis being tested: Infectious agents such as mycoplasma pneumonia and hepatitis A may lead to leukemia. There may be a dose-response relationship in the association between in utero exposure to radiation and childhood leukemia. Paternal smoking has a more powerful effect on childhood cancer than maternal smoking. EMF exposure may be associated with leukemia.

Study #3 findings: One study in Greece indicated that infants exposed in utero to radiation had a higher incidence of leukemia and that there was a positive dose-response relationship between incidence and radioactivity in the region. Most epidemiological studies of parental smoking have indicated positive associations between paternal, rather than maternal, smoking and childhood cancer. This may be due to germ cell mutations in the father that develop before conception. Studies have not been able to show a significant association between EMF exposure and childhood cancer. It is probable that prenatal and postnatal exposure to low frequency EMFs through power lines or small appliances is not strongly associated with an increased risk of leukemia. No individual data has yet been collected to support or refute hypotheses involving the association between infectious agents and childhood cancer. The etiology of most cancers is unknown. The prenatal period is emerging as the etiologically relevant window for many childhood, particularly infant, cancers. The association between maternal exposure to farm animals and development of brain tumors in children needs further research. Medical exposure to medications such as metronizadole in utero may be linked to childhood cancer. One study found an increased risk of neuroblastomas in children exposed to this drug in utero. Further studies may be needed given some outcomes may not appear until later in childhood or adolescence.

Hypothesis #10: Exposure to infectious agents/viruses may increase the risk of childhood cancers, including brain tumors, and may increase the risk of lung cancer in adulthood.

General Information Related to Hypothesis #10

- **Prevalence and incidence of brain tumors in children:** Brain tumors account for 20% of all childhood cancers. Between 1973 and 1994, incidence rates of childhood brain tumors (CBTs) increased 29%.[33]
- **Frequency/load of exposure to infectious agents:** Children of parents whose occupation is associated with higher exposure to animal viruses (e.g., veterinarians, farmers) may be at higher risk.[34]
- **Findings from recent research (targeted search):** Information reported in the following three studies contributed to the above-mentioned hypothesis.

Study #1: Alexander FE. Clusters and clustering of childhood cancer: A review. European Journal of Epidemiology 1999;15(9):847-52.

Study #1 hypothesis being tested: Infectious processes may play a role in clustering of childhood cancer.

Study #1 findings: The authors note that despite data that suggests an infectious process associated with childhood leukemia, no definitive causative agent has been identified leading to childhood leukemia. Some studies have pointed to a possible infectious process leading to childhood leukemia and clustering of childhood cancer. No causal factor, however, has been identified that explains clustering. The authors suggest that, in order to explain cancer clusters, it will be helpful to identify causes of cancer through large national case-control studies and determine whether clustering is due to a single cause or due to chance aggregation of cases with separate causes.

Study #2: Yeni-Kmishian H, Holly EA. Childhood brain tumours and exposure to animals and farm life: a review. Paediatric and Perinatal Epidemiology 2000;14:248-256.

Study #2 hypothesis being tested: Fetal and/or childhood exposure to animal viruses through contact with farm animals and pets can induce brain tumor formation.

Study #2 findings: The authors found that out of five studies of childhood farm residence or exposure of mother or child to farm animals, four reported elevated risk for CBT. However, farm exposures are uncommon in the population studied and population attributable risks for CBT would be minimal. Small numbers of subjects in subgroups of exposed individuals provided inadequate power to rule out chance as a possible factor in most studies. Exposures on a farm are many and varied, and putative

[33] Yeni-Kmishian H, Holly EA. Childhood brain tumours and exposure to animals and farm life: a review. Paediatric and Perinatal Epidemiology 2000;14:248-256.

[34] Ibid.

elevated risk of CBT resulting from farm animal exposures could possibly be related to unmeasured pesticide exposure. Despite inconclusive evidence, the reported excess risk for CBT with maternal exposures to farm life is supported by parental occupational studies. Parental occupation in agriculture has been associated with other childhood cancers, such as leukemia. Also, veterinarians and farmers have significantly higher rates of brain tumors when compared with the general U.S. population. Farm residence and animal exposure place children at risk of contact with various viruses and parasites. Humans may be infected with animal viruses that may be related to brain tumorigenesis. An association between maternal or childhood exposure to neurocarcinogenic viruses from farm life and CBT needs further investigation.

Study #3: Ross JA, Swensen AR. Prenatal epidemiology of pediatric tumors. Current Oncology Reports 2000;2(3):234-41.
(Note: This study is cited under childhood cancers and other exposures – EMFs and paternal/maternal smoking.)

Study #3 hypothesis being tested: Infectious agents such as mycoplasma pneumonia and hepatitis A may lead to leukemia. There may be a dose-response relationship in the association between in utero exposure to radiation and childhood leukemia. Paternal smoking has a more powerful effect on childhood cancer than maternal smoking. EMF exposure may be associated with leukemia.

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